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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/708,953	04/02/2004	Itzhak Bentwich	050992.0201.04USCP	2952

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EXAMINER	
PITRAK, JENNIFER S	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/708,953	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/27/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Remarks

In the response filed 05/27/2008, Applicant amended claim 18, submitted arguments, and submitted a declaration of Dr. Pilpel. The declaration of Dr. Pilpel under 37 C.F.R. § 1.132 received on 05/27/2008 has been considered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 18-29 are pending and are under examination

Priority

The instant claims have the benefit of the instant filing date, 04/02/04, as indicated in the 11/28/2007 Office Action.

Claim Rejections - 35 USC § 102 – WITHDRAWN

The amendments to the claims have obviated the rejection of claims 18 and 24 under 35 U.S.C. 102(b). Therefore, the rejection is withdrawn as being clearly anticipated by Hood, *et al.* (US PGPUB 2002/0150891).

Claim Rejections - 35 USC § 101/112 - MAINTAINED

Claims 18-29 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. This rejection is maintained for the reasons of record and as further explained.

The claims are drawn to isolated nucleic acid molecules 16-120 nucleotides in length , wherein the sequence comprises 16 or more nucleotides of SEQ ID NO: 2240728. The claims are also to the isolated nucleic acid molecule wherein the 16 or more nucleotides comprise SEQ ID NO: 8385. The claims are also to vectors comprising such nucleic acid molecules. According to the instant specification, the claimed molecules are "genomic address messenger" or "GAM" genes, which are related to miRNAs (p.17, paragraphs [0022] and [0023]). Also, according to the specification, the GAMs specifically inhibit translation of one or more target genes by hybridization to an untranslated region (UTR) of a target mRNA (p.20, paragraph [0032]. The specification generally states that the GAMs may be useful for downregulating expression of genes including disease-associated genes.

The specification provides no evidence that any of the predicted nucleic acid molecules, including SEQ ID NO: 2240728, actually function as a miRNA-like molecule or otherwise. The specification provides no evidence that the nucleic acid molecules exist endogenously. As was known at the time of filing, prediction of miRNAs yielded predictions that were not valid, i.e., many predicted miRNAs had no biological function. For example, John, *et al.* (2004, PLoS Biology, v.2,:1862-1879, of record) reported prediction of miRNA targets using an algorithm based on several factors including sequence complementarity between miRNA and target site and evolutionary conservation of the target sequence (see p.1864, second paragraph). The authors commit most of pages 1864-6 and Table S8 of their summary article to explaining their methods of validating predicted miRNA targets, specifically noting that "only a small number of target sites of target genes regulated by miRNAs have been experimentally verified," (p.1864, last paragraph). At p.1865 in the sixth paragraph, the authors report that "The percentage of false positives for target transcripts with more than two, three, and four sites is 39%, 30%, and

24%, respectively," and that the false-positive rate for single sites is about 35%. Furthermore, the authors indicate that the usefulness of their prediction method is to facilitate focused experiments (abstract) and to facilitate evaluation of the predictions (p.1864, fifth paragraph). Thus, although miRNA target predictions were accomplished, the real-life value of each predicted miRNA needed to be assessed by experimentation. Therefore, the instantly claimed nucleic acid molecules have no known value or utility except as one of millions of possibly useful molecules and therefore lack credible utility.

Claims 18-29 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to arguments

Applicant argues that, in contrast to the basis of the decision in *Fisher* 421 F.3d at 1371, the current application provides specific utility for the disclosed and claimed nucleic acids (p.4 of response). Specifically, Applicant argues that while the ESTs in *Fisher* were not targeted to a particular gene, each of the presently disclosed nucleic acids is capable of modulating a specific gene transcript and, furthermore, that the claimed microRNA-related sequences specifically target mRNA transcripts of the SRY gene and regulate the translation of mRNAs from the specific target gene SRY. These arguments are not persuasive. While it is agreed that, in contrast to the case in *Fisher*, the instant application provides that SEQ ID NO: 8385 has complementarity to SRY and appears to be a predicted miRNA, it is expressly not agreed that (1)

the predicted SEQ ID NO: 8385 results from the processing of the predicted precursor molecule having SEQ ID NO: 2240728 and (2) that SEQ ID NO: 8385 actually targets and modulates SRY. As indicated in the rejection set forth above, the art clearly teaches that many miRNAs are predicted, but that only a percentage of predicted miRNAs actually exist and actually function to downregulate their predicted target gene expression. Applicant asserts that the claimed sequences regulate the translation of mRNAs from the specific target gene SRY (paragraph 3 on p.4 of response). However, neither the art nor the specification support such an assertion. The art and specification support the prediction of possible miRNAs for regulating target gene expression, and further that these predictions must be validated to conclude the actual existence and function of such predicted molecules.

In section (2) on pages 4-5 of the response, Applicant further argues that, whereas in *Fisher*, the court concluded that the claimed ESTs were objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end, the instant application discloses that the claimed molecules may be used to bind and regulate SRY mRNA transcripts. Applicant then further explains the function of the SRY gene. This is not persuasive because, just as in the *Fisher* case, the instant case also presents objects upon which scientific research could be performed, predicted miRNAs, with no assurance that the claimed miRNA-like molecules actually exist and/or function to downregulate SRY expression. The claimed sequences are predicted miRNA-like molecules, the existence and function of which is subject to validation as described above.

On pages 5-6 of the response, Applicant argues that the record clearly shows that one of ordinary skill in the art would believe that the claimed nucleic acids may be used to modulate expression of the specific mRNA targets and presents Dr. Pilpel's declaration as support for such

argument. Applicant states that Dr. Pilpel concludes that the miRNA of SEQ ID NO: 8385 is likely to inhibit expression of the protein encoded by the target gene SRY in view of the characteristics of miRNA:mRNA binding properties. This is not persuasive because, again, SEQ ID NO: 8385 is a predicted miRNA-like molecule, the existence and function of which has yet to be determined.

Applicant further argues that Dr. Pilpel's declaration indicates that SEQ ID NO: 8385 and its respective SRY target sequences are consistent with miRNA and target mRNAs predicted by the algorithms available in the art, namely TargetScan and miRanda (see section (b) on page 6 of response). This is not persuasive because it is precisely this art, to which Applicant refers, that teaches the false positive rates of between 22-35% for miRNA predictions. This false positive rate indicates that although a sequence, such as SEQ ID NO: 8385 may look like a miRNA, whether or not it is a miRNA remains to be determined experimentally.

Finally, Applicant argues at page 7 of the response that SRY is a credible target for trans-acting regulatory elements specifically because SEQ ID NO: 8385 is capable of binding SRY with 12 of 22 nucleotides of complementarity. This is not persuasive because, as indicated above, it is unknown whether SEQ ID NO: 8385 is actually a functional miRNA, let alone that it will target and modulate SRY.

Thus, the rejection of claims 18-29 under 35 U.S.C. § 101 for lacking credible, specific, and substantial utility and, therefore, lacking enablement under 35 U.S.C. § 112 is maintained.

Claim Rejections - 35 USC § 112 - WITHDRAWN

The amendments to the claims have obviated the rejection of claims 18-29 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Therefore, the rejection is withdrawn.

Claim Rejections - 35 USC § 112 - MAINTAINED

Claims 18-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to the nucleic acid molecules as described above. The function of the claimed molecules is not known nor demonstrated per the instant specification. Although the instantly claimed molecules are described to function like miRNAs, there is no support for such a function in the specification nor in the prior art. Furthermore, as previously described above under the 35 USC §101/112 rejection, the utility of the endogenous molecules of the instant application is not known and there is significant error in prediction of miRNA-like molecules and their targets. Thus, the claims are not enabled.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak, PhD
Examiner
Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635